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Drug Dosing Considerations in Patients with Acute Kidney Injury and Chronic Kidney Disease

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CHAPTER OUTLINE

Acute kidney injury (AKI) and chronic kidney disease (CKD) can affect multiple organ systems, and these physiologic changes have been associated with profound alterations in the pharmacokinetics (PK) and pharmacodynamics (PD) of many drugs.[1,2] Clinicians must assess kidney function and consider how kidney function alters the disposition of drugs and their active or toxic metabolites. The number of patients with AKI and CKD and end-stage kidney disease (ESKD) has increased in the last 10 years.[3,4] Independent of injury or disease, kidney function tends to decrease with age, and older patients constitute an ever-increasing group for whom the optimization of drug therapy is crucial.[5] The widespread use of alternative renal replacement therapies for treating AKI (e.g., continuous venovenous hemodiafiltration) and ESKD (frequent and/or nocturnal hemodialysis or hemodiafiltration) during the last decade mandate an understanding of their influences on drug disposition.[6] When comparing outcomes of different dialytic modalities, rarely has the effect on drug disposition been considered.[3,6-8] Although innovation in peritoneal dialysis has been more modest, few studies have examined the effects of newer adequacy targets, or the use of nondextrose-containing peritoneal dialysates on drug disposition.

Data on the use of many drugs in patients with CKD, as well as the impact of dialysis, are often limited or absent at the time of regulatory approval. Patients with moderate to advanced CKD are typically excluded from participation in major safety and efficacy studies required for drug registration. Although regulatory authorities now require a pediatric investigation plan as a routine part of drug development, they have not yet responded to the challenge of ensuring robust data for patients with impaired kidney function.[1] Indeed, significant differences exist with respect to the means of assessment and classification of the degree of impaired kidney function.[9] Thus, some recommendations are not concordant as to whether drug dose adjustment is necessary at all.[10] The availability of robust and readily applicable information to guide prescribing for patients with kidney disease remains imprecise and relies on interpolation, extrapolation, and estimation.[11,12] Optimization of CKD and AKI patient care is dependent on the clinician's knowledge of basic biochemical and physiologic understanding of drug disposition as well as individual experience with the effects of renal replacement therapies (RRTs) on drug and metabolite removal.

In the 1970s, with the advent of specific and sensitive analytic techniques, the pharmaceutical industry began to investigate the relationship of kidney function to the pharmacokinetics and pharmacodynamics of the drugs they had in development. Until the 1990s, there remained no

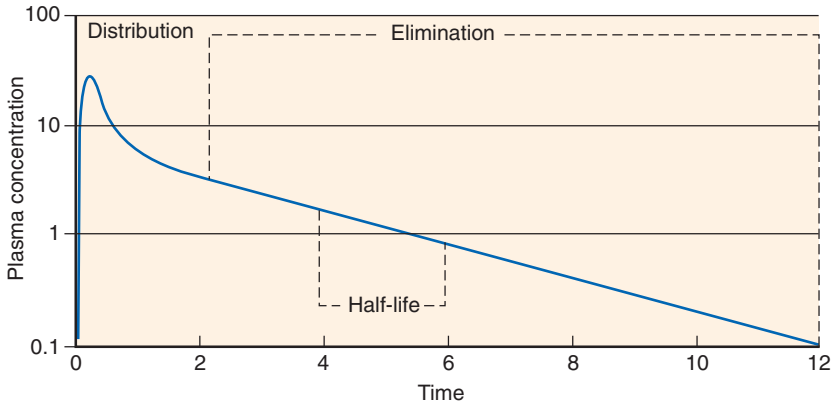

Figure 64.1 Distribution and elimination of a drug after intravenous administration.

regulatory guidance or clinical consensus for when investigations should be conducted and with what degree of rigor. Thus, much of the data on the PK of drugs in patients with kidney disease was the result of clinician-initiated, postmarketing studies. These resulted in the publication of inconsistent and, in some cases, conflicting recommendations regarding adjustments in drug dose or frequency of administration.[1] Critical issues include characterization of the degree of impact of AKI or CKD on a drug's disposition, pharmacodynamics, and/or dependence on pharmacogenetics, identification of the most reliable index of kidney function for drug dosing, determination of the desired therapeutic endpoints, significance of risks associated with the accumulation of drug and/or metabolite concentrations, predictive performance of various methodologies to calculate the desired dosage regimen, and quantification of the influence of RRTs on drug disposition.

In this chapter, the influence of AKI and CKD on drug pharmacokinetic properties is characterized, and a guide for individualizing drug therapy in patients with AKI and CKD is presented, along with dosage recommendations for many commonly used drugs. The role of pharmacodynamic measures alone or in combination with pharmacokinetics, as well as pharmacogenetic testing in drug dosage regimen design, is discussed. The impact of maintenance dialysis for ESKD and continuous RRT (CRRT) for patients with AKI on drug disposition are discussed, and dosage recommendations for most critical drugs are presented.

EFFECTS OF AKI AND CKD ON DRUG DISPOSITION

Pharmacokinetics describes the time course of drug absorption, distribution, metabolism, and elimination. Pharmacodynamics provides a characterization of the complex interaction of drug concentrations, receptor-drug interactions, mechanism of action, and clinical factors, such as concurrent diseases and degree of organ dysfunction on patients' response to drug therapy. The combination of PK and PD drug characteristics allows clinicians with foundational information to make rational prescribing decisions.

When given intravenously (IV), a rapid decrease in the plasma concentration follows an initial high drug concentration. This decrease occurs as the drug distributes from the plasma into the extravascular space and beyond. During the terminal elimination phase, drug concentrations in plasma are in equilibrium with concentrations in body tissues (Figure 64.1). The rate and extent of drug absorption and distribution and rate of drug elimination may be ascertained by mathematical analysis of the serum or plasma concentration data collected over an appropriate time interval. The terminal elimination half-life of a drug is the time required for the plasma concentration to decline by 50%; this it can be determined from the slope of the elimination phase of the plot of serum or plasma drug concentration versus time after the drug is ingested or injected. By comparing PK data from patients with normal kidney function with data from patients with impaired kidney function, rational drug dosing regimens may be proposed.[11-13]

ABSORPTION

Drugs given IV enter the central circulation directly and generally have a rapid onset of action. Drugs given by other routes must first pass through important organs of elimination before entering the systemic circulation; thus, a smaller proportion of the drug reaches the systemic circulation. In many cases, only a fraction of the administered dose may reach the circulation and become available at the site of drug action. Even drugs given IV and by inhalation must pass though the lungs before reaching arterial blood. Similar to other organs, the lungs remove substantial amounts of some agents. For drugs administered orally, the rate and extent of gastrointestinal (GI) absorption are important considerations. Absorption has been characterized by determining the maximum attained serum or plasma concentration (C_{max}), as well as the time after ingestion when the C_{max} was observed (T_{max}). Differences in these two parameters among patient groups were historically considered evidence of altered GI absorption when actually the bioavailability may have been unchanged.[14] The bioavailability of a drug depends on the extent of metabolism during its first pass through the GI tract and liver before reaching the systemic circulation. The absolute bioavailability is determined by comparing the area under the serum/plasma concentration-time curve (AUC) after oral administration to that observed after IV administration.

When this measure of bioavailability was assessed, there were very few drugs shown to be affected by the presence of CKD or AKI.[15]

First-pass biotransformation may also occur in the gut; bioflavonoids in grapefruit juice can inhibit cytochrome P 450 (CYP) 3A4 and noncompetitively inhibit the metabolism of drugs metabolized by this enzyme. This grapefruit juice–CYP3A4 interaction was first noted with the calcium channel blocker felodipine.[16] This interaction also increases the bioavailability of cyclosporine by as much as 20%.[17] A wide variety of other drugs are similarly affected, including several medications used for depression and anxiety (e.g., selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs]) and statins.[18] Herbal medicine (e.g., hypericin) can activate the adenosine triphosphate (ATP)–binding cassette (ABC) transporter or P-glycoprotein (multidrug resistance) transporter in gut mucosa, leading to reduced drug absorption.[19]

Although GI symptoms are common in patients with ESKD, little specific information about alimentary function is available. The salivary concentration of urea increases when urea accumulates in plasma. Ammonia forms from urea in the presence of gastric urease and buffers gastric acid, increasing gastric pH. The ammonia is absorbed and converted to urea again by the liver. The gastric alkalinizing effect of this internal urea-ammonia cycle decreases the absorption of drugs that are best absorbed in an acidic environment. Drug malabsorption may be further aggravated by the increased use of various therapies to reduce gastric acidity and/or reduce phosphate absorption, especially in patients who are dialysis-dependent.[14,20,21] The resultant chelation and formation of nonabsorbable complexes reduce the bioavailability of some drugs, including several antibiotics and digoxin.

The processes of GI drug absorption are complex, may be saturable and dose-dependent, and are more variable in patients with ESKD than in those with normal kidney function.[22] Gastroparesis, commonly observed in patients with diabetes mellitus, many of whom also have CKD, prolongs gastric emptying and delays drug absorption; that is, T_{max} is observed to be delayed. Conversely, diarrhea decreases gut transit time (T_{max} is shortened and diminishes drug absorption by the small bowel). Gut mucosal integrity becomes impaired across the spectrum of CKD, as evidenced by increasing levels of circulating translocated endotoxins.[23]

DISTRIBUTION

The volume of distribution of a drug does not necessarily correspond to a specific anatomic space. Rather, the volume of distribution is a mathematical construct based on the plasma concentration achieved following the IV administration of a given dose of a drug. Agents that are highly protein-bound and those that are water-soluble tend to be restricted to the vascular compartment and extracellular fluid (ECF) space, respectively, and thus have volumes of distribution less than 0.20 L/kg. Highly lipid-soluble drugs and those extensively bound to tissues often exhibit volumes of distribution in excess of 1 L/kg. The drug distribution volume of highly water-soluble or protein-bound drugs may be increased in patients with AKI or CKD if edema and/or ascites is present (Table 64.1).[2,5,13,15,24] Drug distribution is one of the most important and complicated factors to quantify in patients with AKI. There is a fine balance between detrimental fluid overload and adequate hydration to preserve and optimize perfusion and function. Critically ill patients should be managed in a slightly negative fluid balance after initial adequate fluid resuscitation has been achieved.[25-29] If patients are volume-expanded, the administration of the usual doses of many drugs will result in inadequately low plasma concentrations.

Table 64.1 Volume of Distribution of Selected Drugs in Patients with Normal Kidney Function and Those on Dialysis

Drug	Normal (L/kg)	Stage 5 CKD (L/kg)	Change from Normal (%)
Increased			
Amikacin	0.20	0.29	45
Cefazolin	0.13	0.17	31
Cefoxitin	0.16	0.26	63
Ceftriaxone	0.28	0.48	71
Cefuroxime	0.20	0.26	30
Doripenem	0.25	0.47	88
Dicloxacillin	0.08	0.18	125
Erythromycin	0.57	1.09	91
Furosemide	0.11	0.18	64
Gentamicin	0.20	0.32	60
Isoniazid	0.6	0.8	33
Minoxidil	2.6	4.9	88
Phenytoin	0.64	1.4	119
Trimethoprim	1.36	1.83	35
Vancomycin	0.64	0.85	33
Decreased			
Chloramphenicol	0.87	0.60	–31
Digoxin	7.3	4.0	–45
Ethambutol	3.7	1.6	–57

Data from references 2, 5, 13, and 15.

The distribution volume of drugs may be altered by fluid removal during dialysis.[30] Changes in body cell mass (nonfat, nonwater, nonbone mineral mass) commonly occur over time in patients on dialysis,[31] resulting in sarcopenia. Failure to detect a reduction in body cell mass may lead to inappropriate maintenance of the same dry weight and drug dosage regimen, despite a real increase in total body water[32] (and thus the distribution volume of several drugs).

Finally, the method used to calculate the volume of distribution may be influenced by impaired kidney function. The three most commonly used volume of distribution terms are volume of the central compartment (V_c), volume of the terminal phase (V_β and V_{area}), and volume of distribution at steady state (V_{ss}). The V_c for many drugs approximates extracellular fluid volume and thus may be increased or decreased by acute changes. Oliguric acute renal failure is often accompanied by fluid overload and a resultant increased V_c for many drugs. The V_{area} or V_β represents the proportionality constant between plasma concentrations in the terminal elimination phase and the amount of drug remaining in the body. V_β is affected by distribution characteristics and by the terminal elimination rate constant. V_β

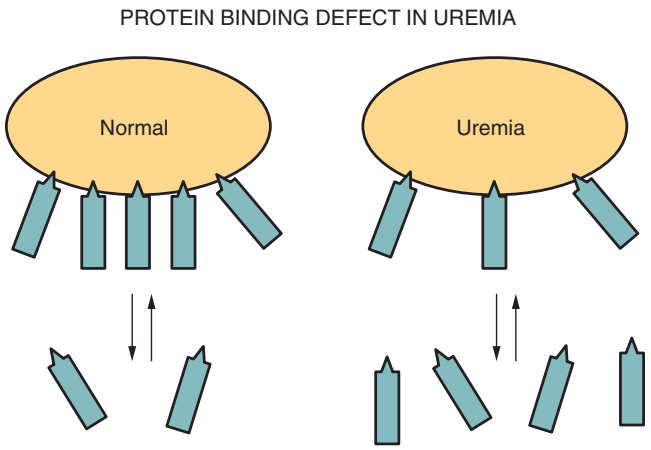

Figure 64.2 Protein-binding defect in uremia. Displacement of the drug from its binding site by an accumulation of undefined uremic toxins or a uremia-induced conformational change in the binding site geometry results in more free drug in the plasma.

and V_{ss} will often be similar in magnitude, with V_β being slightly larger. Because V_{ss} has the advantage of being independent of drug elimination, it is the most appropriate volume term to use when it is desirable to compare drug distribution volumes between patients with renal insufficiency and those with normal renal function.[33]

Alterations of plasma protein binding in patients with CKD can also affect drug action. The volume of distribution of a drug, quantity of unbound drug available for action, and degree to which the agent is eliminated by hepatic or renal excretion are all influenced by protein binding. Drugs that are protein-bound attach reversibly to albumin or α1-glycoprotein in plasma (Figure 64.2). Whereas organic acids bind to a single binding site, organic bases probably have multiple sites of attachment.[34,35]

Protein-bound organic acids such as hippuric acid, indoxyl sulfate, and 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid (CMPF) accumulate in advanced CKD and decrease the protein binding of many acidic drugs.[36-38] A combination of decreased serum albumin concentration and reduction in albumin affinity for the drug reduces protein binding in dialysis-dependent patients. Even when the plasma albumin concentration is normal, the protein-binding defect of some drugs correlates directly with the level of azotemia and may be corrected with dialysis.[5,8,34] Binding affinity is influenced by changes in the structural orientation of the albumin molecule or by the accumulation of endogenous inhibitors of protein binding that compete with drugs for their binding sites.[34]

The unbound fraction of several acidic drugs are increased in CKD because of impaired plasma protein binding. Toxicity can occur if the total plasma concentration of these drugs is pushed into the therapeutic range by increasing the dose, wherein the free (active) concentration may be in the supratherapeutic range. For such drugs, unbound plasma concentrations should be measured to guide therapy. The need to measure unbound drug concentrations applies especially to drugs with very narrow therapeutic ranges, such as phenytoin.[39] Predicting the clinical consequences of altered protein binding is difficult. Although decreased binding results in more unbound drug being available at the site of drug action or toxicity, the distribution volume is increased, resulting in lower plasma concentrations after a given dose. More unbound drug is available for metabolism and excretion, which increases the clearance and decreases the half-life of the drug in the body. Drugs with decreased protein binding in patients on dialysis are listed in Table 64.2.

Table 64.2 Unbound Fraction of Selected Drugs in Patients with Normal Kidney Function and End-Stage Kidney Disease (ESKD)

Drug	Normal Patient	ESKD Patient	Change from Normal (%)
Acidic Drugs			
Abecarnil	4	15	275
Azlocillin	62.5	75	20
Cefazolin	16	29	81
Cefoxitin	27	59	119
Ceftriaxone	10	20	100
Clofibrate	3	9	200
Dicloxacillin	3	9	200
Diflunisal	12	44	267
Doxycycline	12	28	133
Furosemide	4	6	50
Methotrexate	57.2	63.8	12
Metolazone	5	10	100
Moxalactam	48	64	33
Pentobarbital	34	41	21
Phenytoin	10	21.5	115
Salicylate	8	20	150
Sulfamethoxazole	34	58	71
Valproic acid	8	23	188
Warfarin	1	2	100
Basic Drugs			
Decreased			
Bepridil	0.3	0.1	–67
Clonidine	55.6	47.6	–14
Disopyramide	32	28	–13
Propafenone	3.4	2.4	–29
Increased			
Amphotericin B	3.5	4.1	17
Chloramphenicol	45	64	42
Clonazepam	13.9	16	15
Diazepam	2	8	300
Fluoxetine	5.5	6.5	18
Ketoconazole	1	1.5	50
Prazosin	6	10.1	68
Rosiglitazone	0.16	0.22	38
Triamterene	19	43	126

METABOLISM

The disposition of drugs metabolized by the liver may be altered by changes in plasma protein binding. The systemic clearance of a highly protein-bound drug with a low hepatic extraction ratio depends on the simultaneous effects of AKI or CKD on protein binding and intrinsic metabolic drug clearance. Because the effects of severe CKD on these two

factors offset each other in terms of total systemic clearance, the lowest total systemic clearance is not seen in patients with ESKD but rather occurs in patients with moderate to severe CKD. The systemic clearance of drugs with a high hepatic extraction ratio is not thought to be as susceptible to the effect of CKD as that of drugs with a low extraction ratio.[40]

Many active or toxic metabolites depend on the kidneys for their removal from the body. The accumulation of these metabolites in patients with impaired kidney function (AKI and CKD) can explain in part the high incidence of adverse drug reactions in this patient population. For example, although the liver usually rapidly metabolizes morphine, it is excreted mainly in the urine because its active metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) readily cross the blood-brain barrier and bind to opiate receptors, exerting strong analgesic effects. In patients with CKD, morphine itself is metabolized more slowly, and these active metabolites increase, making prolonged narcosis and respiratory depression more likely.[41,42] Similarly, the biotransformation of meperidine results in the production of normeperidine, a more polar metabolite that is normally rapidly excreted in the urine. Normeperidine has little to no analgesic activity but lowers the seizure threshold. In patients with impaired kidney function, repeated doses of meperidine may result in the accumulation of this potentially toxic metabolite, with resultant seizures.[43] Table 64.3 lists some drugs that form active or toxic metabolites in CKD patients and have been associated with adverse outcomes.

ALTERATIONS OF CYTOCHROME P450 ENZYME ACTIVITY

A decrease in the renal clearance of drugs in patients with CKD is well appreciated. However, there is now preclinical and emerging clinical evidence suggesting that advanced CKD (stages 4 and 5) may lead to reductions in the nonrenal clearance of many medications as the result of alterations in the activities of uptake and efflux transporters, as well as CYP enzymes, in the liver and other organs (Table 64.4).[35,44-49] The effect(s) of AKI and CKD on nonrenal drug clearance appear to depend on whether the reduction in renal function is acute or chronic in nature—and likely stronger in CKD.

Preservation of nonrenal metabolic clearance has been observed early in the course of AKI,[50-53] and thus drug dosing schemes extrapolated from those with stable CKD may therefore result in ineffectively low drug concentrations. Furthermore, failure to appreciate that changes in serum creatinine levels are not an accurate marker of the glomerular filtration rate (GFR) early in AKI may lead to further dosing errors. The first reports of nonrenal clearance of drugs being affected by AKI came from the observation that the residual nonrenal clearances for vancomycin, meropenem, and imipenem were higher in patients with AKI compared to patients with CKD, who had comparable creatinine clearance (CrCl).[51-53]

Most of the direct evidence on metabolism in the presence of AKI has been derived from investigations in animal models. A number of drugs have been studied in a variety

Table 64.3 Drugs with Pharmacologically Active Metabolites that May Affect Efficacy or Toxicity in Patients with Severe Chronic Kidney Disease

Parent Drug	Metabolite	Pharmacologic Activity of Metabolites
Acetaminophen	*N*-Acetyl-*p*-benzo-quinoneimine	Responsible for hepatotoxicity
Allopurinol	Oxipurinol	Metabolite primarily responsible for suppression of xanthine oxidase
Azathioprine	Mercaptopurine	All immunosuppressive activity resides in the metabolite.
Cefotaxime	Desacetyl cefotaxime	Similar antimicrobial spectrum, but 10% to 25% as potent
Chlorpropamide	2-Hydroxychlorpropamide	Similar in vitro insulin-releasing activity
Clofibrate	Chlorophenoxyisobutyric acid	Primarily responsible for hypolipidemic effect and direct muscle toxicity
Codeine	Morphine-6-glucuronide	Possibly more active than parent compound; may contribute to prolonged narcotic effect in renal failure patients
Imipramine	Desmethylimipramine	Similar antidepressant activity
Ketoprofen	Ketoprofen glucuronide	Accumulation of acyl glucuronide may worsen toxic effects (GI disturbances, impairment of kidney function)
Meperidine	Normeperidine	Less analgesic activity than parent, but more central nervous system stimulatory effects, epileptogenic
Morphine	Morphine-6-glucuronide	Possibly more active than parent compound; may contribute to prolonged narcotic effect in ESKD
Mycophenolic acid	Mycophenolic acid glucuronide	Lacks pharmacologic activity but may be associated with dose-limiting (GI) side effects
Procainamide	*N*-Acetyl procainamide	Distinct antiarrhythmic activity; mechanism different from that of parent compound
Sulfonamides	Acetylated metabolites	Devoid of antibacterial activity; elevated concentrations associated with increased toxicity
Theophylline	1,3-Dimethyl uric acid	Cardiotoxicity has been demonstrated.
Zidovudine	Zidovudine triphosphate	Primarily responsible for antiretroviral activity

Table 64.4 Major Pathways of Nonrenal Drug Clearance (Cl_{NR})

Cl_{NR} Pathway	Selected Substrates
Oxidative Enzymes	
CYP1A2	Polycyclic aromatic hydrocarbons, caffeine, imipramine, theophylline
CYP2A6	Coumarin
CYP2B6	Nicotine, bupropion
CYP2C8	Retinoids, paclitaxel, repaglinide
CYP2C9	Celecoxib, diclofenac, flurbiprofen, indomethacin, ibuprofen, losartan, phenytoin, tolbutamide, *S*-warfarin
CYP2C19	Diazepam, *S*-mephenytoin, omeprazole
CYP2D6	Codeine, debrisoquine, desipramine, dextromethorphan, fluoxetine, paroxetine, duloxetine, nortriptyline, haloperidol, metoprolol, propranolol
CYP2E1	Ethanol, acetaminophen, chlorzoxazone, nitrosamines
CYP3A4/5	Alprazolam, midazolam, cyclosporine, tacrolimus, nifedipine, felodipine, diltiazem, verapamil, fluconazole, ketoconazole, itraconazole, erythromycin, lovastatin, simvastatin, cisapride, terfenadine
Conjugative Enzymes	
UGT	Acetaminophen, morphine, lorazepam, oxazepam, naproxen, ketoprofen, irinotecan, bilirubin
NAT	Dapsone, hydralazine, isoniazid, procainamide

Data from references 35, 44-49.

of AKI models. AKI is a heterogenous insult that is often part of multisystem failure of cellular respiration and can have in various consequences.[54-57] CYP enzymes are affected by AKI, and the extent of these effects may depend on the mechanism of experimental AKI. Definitive conclusions on the pharmacokinetics of metabolized medications in AKI remain hampered by the clinical complexity and potential confounders; hypoxia, decreased protein synthesis, competitive inhibition from concomitant medications, and decreased hepatic perfusion could also contribute to the reduced clearance.

In humans with CKD, the activities of CYPs appear to be relatively unaffected.[46,49,58] It has been reported that CYP3A4 activity is reduced,[45-47,49] but recent studies have indicated that organic anion transporting polypeptide (OATP) uptake activity is decreased. Thus, the perceived changes in CYP3A4 activity were likely due to altered transporter activity, not to an alteration in CYP activity. The reduction of nonrenal clearance of several drugs that exhibit overlapping CYP and transporter substrate specificity in patients with stage 4 or 5 CKD supports this premise. These studies must be interpreted with caution, however, because concurrent drug intake, age, smoking status, and alcohol intake were often not taken into consideration. Furthermore, pharmacogenetic variations in drug-metabolizing enzymes that may have been present in the individual before the onset of AKI or CKD must also be considered.

RENAL EXCRETION

Renal clearance (Cl_R) of a drug is the composite of the GFR, tubular secretion, metabolism, and reabsorption $[(Cl_R = (GFR \times f_u) + (Cl_{secretion} + Cl_{metabolism} - Cl_{reabsorption})]$, where f_u is the fraction of the drug unbound to plasma proteins. Drug elimination by filtration occurs by a pressure gradient, whereas tubular secretion and reabsorption are bidirectional processes that involve carrier-mediated renal transport systems.[49,59-61] Renal transport systems have been broadly classified on the basis of substrate selectivity into anionic and cationic renal transport systems, which are responsible for the transport of a number of organic acidic and basic drugs, respectively.[35,49] Several drugs are actively secreted by one or more of these transporter families, including organic cationic (e.g., famotidine, trimethoprim, dopamine), organic anionic (e.g., ampicillin, cefazolin, furosemide), nucleoside (e.g., zidovudine), and P-glycoprotein transporters (e.g., digoxin, vinca alkaloids, steroids).[52,60] Alterations in filtration, secretion, or reabsorption secondary to CKD may have a dramatic effect on drug disposition. For drugs that are primarily filtered, a reduction in GFR will result in a proportional decrease in renal drug clearance.

PHARMACOGENOMICS

Over the last 2 decades, genome-wide analyses have identified genetic variants that are associated with the risk of several diseases,[62,63] although most confer a very low relative risk and have low discriminatory and predictive values.[64,65] The variability in how patients respond to drug treatments is a consequence of alterations in pharmacokinetics and pharmacodynamics, as outlined in this chapter, as well as differences in their genotypes and/or phenotypes.[63,66-72] The validity of phenotyping cocktails and their correlation with genotyping data are still in need of clarification.[73] Genotyping information is becoming more widely available than phenotyping data by clinicians and patients and this is bringing in demands for a more individualized approach to pharmacotherapy. Genotypic characterization now serves as the basis for dosing recommendations for some drugs,[74-77] and more than 120 U.S. Food and Drug Administration (FDA)–approved drugs have pharmacogenomic

information in their labeling, including fluoropyrimidines, codeine, SSRIs, tricyclic antidepressants, β-blockers, opiates, neuroleptics, antiarrhythmic agents, and statins.[78] However, the promise of pharmacogenomics has not always translated into improvements in patient care because of the inaccuracy of results and the complexities involved.[79,80] In late 2013, FDA approved four diagnostic, high-throughput, gene-sequencing devices, which represents a significant step forward in the ability to generate genomic information that will ultimately improve patient care.[81] As Collins and Hamburg from the National Institutes of health (NIH) and FDA have stated, "There are many challenges ahead before personalized medicine can be considered truly embedded in health care. We need to continue to uncover variants within the genome that can be used to predict disease onset, affect progression, and modulate drug response."[80] New genomic findings need to be validated before they can be integrated into medical decision making. Physicians and other health care professionals will need support in interpreting genomic data, integrating it into clinical decision making, and applying the results to individual patients. With the right information and support, patients will be able to participate with their physicians in making more informed decisions.

As an example of the complexity of individualizing drug therapy on the basis of genomic information, the commonly prescribed anticoagulant, warfarin, may be considered. Two recently published trials raise significant questions regarding the value of genomic data to guide the initial dosing of this agent.[82,83] A genotype-guided approach to warfarin dosing failed to improve anticoagulation control during the first 4 weeks of treatment, according to the first of the articles.[82] Among 1015 patients assigned to usual care or usual care plus genotype, international normalized ratio (INR) results showed that the mean percentage of time in the therapeutic range at 4 weeks was 45.2% in the genotype-guided group and 45.4% in the usual care group. Moreover, rates of the combined outcome of any INR of 4 or more, major bleeding, or thromboembolism did not differ significantly according to dosing strategy.

The second study reported conflicting results in that pharmacogenetic-based dosing was associated with a slightly but significantly higher percentage of time in the therapeutic INR range, with significantly fewer incidences of excessive anticoagulation (INR ≥ 4.0) in the genotype-guided group. Thus, at present, there are insufficient data indicating a therapeutic benefit related to genomic information in persons with normal kidney function, much less those with CKD or AKI.[84]

PHARMACODYNAMICS

The fundamental concept of pharmacodynamics is described by the Hill equation. This model has been extensively used to optimize the effects of most antimicrobial agents.[85] The principles are applicable to guide the dosing of medications in patients with CKD, as well as those with normal kidney function. In the patient with CKD, the concentration time profile of many drugs is altered, so the dosage regimen predicted will likely be different than the normal regimen. This is because of the prolonged elimination half-life, which results in an increased area under the concentration-time curve. Only rarely has there been evidence of an alteration in the concentration effect relation in patients with AKI or CKD; pharmacokinetic changes predominantly contribute to the need for a modified dosing regimen.

The concentration (C) is the primary driving force that obligates altered dosage regimens to achieve the desired pharmacodynamic targets. The actual effect is a function of the maximum effect and the concentration producing the half-maximum effect. The Hill coefficient (H) is a measure of the sigmoidicity of the effect-concentration correlation:

$$E = \frac{E_{max}}{1-\left(\frac{CE_{50}}{C}\right)^{H}}$$

From this equation, the threshold concentration, which produces 5% of the maximum effect, and the ceiling concentration, which is associated with 95% of the maximum effect, can be derived. The higher the Hill coefficient, the higher the threshold concentration and the narrower is the range of lower and upper target concentrations; this is because the ceiling concentration comes down close to the concentration producing the half-maximum effect (Figure 64.3):

$$CE_{05} = 19^{\frac{-1}{H}} \bullet CE_{50}$$

$$CE_{95} = 19^{\frac{1}{H}} \bullet CE_{50}$$

The difference between the ceiling and threshold concentrations can be measured by multiples of the respective elimination half-life. The ceiling concentration is the upper limit of the targeted peak concentration ($C_{peak} < CE_{95}$), whereas the threshold concentration marks the lower limit

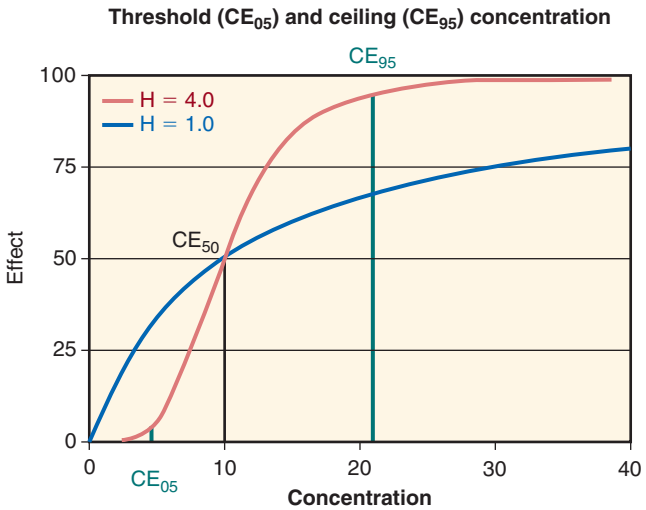

Figure 64.3 Threshold concentration, CE_{05}, producing 5% of the maximum effect and ceiling concentration, CE_{95}, producing 95% of the maximum effect. With a Hill coefficient of H = 1.0, CE_{05} = 0.5 and CE_{95} = 190, whereas for H = 4.0, the threshold is higher, with CE_{05} = 6.0, but the ceiling is much less, with CE_{95} = 21 mg/L.

of effective trough concentration ($Ct_{rough} > CE_{05}$). For a drug with a short half-life ($t_{½}$) and a high Hill coefficient, the therapeutic range of target concentrations can be very small (see Figure 64.3):

$$CE_{05} = CE_{95} \bullet \exp\left(-\frac{\ln(2)}{t_{½}} \bullet t\right)$$

$$t_{ceiling-threshold} = t_{½} \bullet \frac{2}{H} \bullet \frac{\ln(19)}{\ln(2)}$$

$$t_{ceiling-threshold} = t_{½} \bullet \frac{8.5}{H}$$

For the β-lactam ceftazidime, with a short half-life of 2.1 hours in patients with normal kidney function but with a high Hill coefficient of 3.7,[86] the peak to trough or ceiling to threshold time of 5 hours indicates that ceftazidime should be given at least every 6 hours to maximize efficacy. In contrast, and in agreement with the postulated postantibiotic effect, the maximum peak to trough time is estimated as 13 hours for gentamicin, with a half-life of 2 hours but a Hill coefficient of 1.3.[86]

The most important progress in anti-infective dosing has been achieved with the differentiation of drugs with time-dependent actions from drugs with concentration-dependent actions.[87,88] Specific examples are the β-lactam-antibiotics and antiviral drugs with a known time-dependent effect, whereas aminoglycosides and quinolones have a concentration-dependent activity. The threshold and ceiling concentrations are specific functions of the concentration producing the half-maximum effect and the Hill coefficient. Both explain the observation that anti-infective drugs with a time-dependent effect have a significantly higher Hill coefficient than those with a concentration-dependent action.[86] A high Hill coefficient is associated with a high threshold concentration but, simultaneously, with a relatively low ceiling concentration. Thus, it makes no sense to increase the dose of time-dependent anti-infective drugs above the ceiling concentration. In contrast, a low Hill coefficient is associated with a high ceiling concentration and low threshold concentration. Thus, it might increase the effect of concentration-dependent anti-infective drugs to give a high single dose but it is not so critical to extend the administration interval, as proposed for aminoglycosides.[89] Practically, it is necessary to administer anti-infective drugs with a time-dependent action more frequently, whereas anti-infective drugs with a concentration-dependent action should be given with a higher maintenance dose to increase efficacy (Figure 64.4).

Usual measures of the antimicrobial effect, such as the time over minimal inhibitory concentrations (MICs), AUC over MIC, time over MIC, or peak over MIC, can be unified to the following concept. The target concentration should not be less than the threshold concentration for time-dependent effects, but the target concentration could be as high as the ceiling concentration for concentration-dependent effects. A close correlation of the MIC and concentration producing the half-maximum effect has been shown.[86] It was obvious, however, that for concentration-dependent antimicrobial action, the MIC could fall considerably below the concentration producing

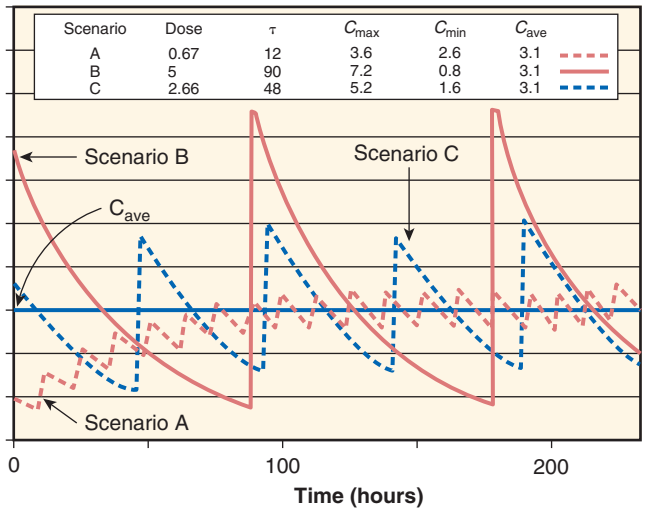

Figure 64.4 Although the average steady-state concentrations (C_{ave}) are identical regardless of which dosage adjustment strategy one decides to use, the concentration-time profile will be markedly different if one changes the dose and maintains the dosing interval (τ) constant (Scenario A), versus changing the dosing interval and maintaining the dose constant (Scenario B) or changing both (Scenario C).

the half-maximum effect ($MIC \ll CE_{50}$). Consequently, it might be more reasonable to compare the bacteriologic MIC with the pharmacodynamic parameter of a threshold concentration:

$$CE_{threshold} = CE_{05} = MIC$$

From the Hill coefficient, one can postulate that the time-dependent action and concentration-dependent action are only the extreme positions of a continuum. Every drug can be considered as concentration-dependent and time-dependent. To overcome resistance, a higher dose might be necessary, because relative resistance can be seen in cases in which a high concentration is required to produce the half-maximum effect. The potency is the inverse concentration producing the half-maximum effect:

$$\text{Potency} = \frac{1}{CE_{50}}$$

This concept distinguishes a relative resistance from an absolute drug resistance. A pathogen with a relative resistance can be made sensitive by increasing the dose.[90-92] Thus, for example, it has been recommended to treat severe infections with resistant strains by increasing the standard meropenem dose to 2000 mg/day, three times daily,[93] or the daptomycin dose to more than 8 mg/kg/day,[94] with careful monitoring of side effects.

ASSESSMENT OF KIDNEY FUNCTION

The standard measure of kidney function for decades has been the GFR.[61] The GFR can be measured using many

Table 64.5 Equations for Estimation of Creatinine Clearance or Glomerular Filtration Rate in Adults with Stable Renal Function

Reference	Equation
Cockcroft and Gault (1976)	Men: $CrCl = (140 - age)IBW/(sCr \times 72)$ Women: $CrCl \times 0.85$
Jelliffe (1973)	Men: $CrCl = 98 - [0.8\ (age - 20)]/sCr$ Women: $CrCl \times 0.9$
MDRD6 (1999)	$eGFRCr = 170 \times (sCr)^{-0.999} \times (age)^{-0.176} \times (0.762$ if patient is female$) \times (1.180$ if patient is black$) \times (BUN)^{-0.170} \times (Alb)^{0.318}$
MDRD4 (2000)	$eGFRCr = 186 \times (sCr)^{-1.154} \times (age)^{-0.203} \times (0.742$ if patient is female$) \times (1.210$ if patient is black$)$
MDRD4-IDMS (2007)	$eGFRCr = 175 \times (sCr)^{-1.154} \times (age)^{-0.203} \times (0.742$ if patient is female$) \times (1.210$ if patient is black$)$
CKD-EPI (2009)	$eGFRCr = 141 \times \min(sCr/\kappa, 1)^{\alpha} \times \max(sCr/\kappa, 1)^{-1.209} \times 0.993^{age} \times (1.018$ if patient is female$) \times (1.159$ if patient is black$)$ • κ is 0.7 for females and 0.9 for males. • α is –0.329 for females and –0.411 for males.. • min is the minimum of sCr/κ or 1. • max is the maximum of sCr/κ or 1.
Larsson et al (2004)	$eGFRCys = 77.24 \times (CysC\ [in\ mg/L])^{-1.2623}$
Macdonald et al (2006)	$\text{Log}_{10}\ eGFRCys = 2.222 + (-0.802 \times \sqrt{CysC\ in\ \frac{mg}{L}}) + (0.009876 \times LM)$
CKD-EPI cystatin C equation (2012)	$eGFRcys = 133 \times \min(sCys/0.8, 1) - 0.499 \times \max(sCys/0.8, 1) - 1.328 \times 0.996^{age}$ ($\times$ 0.932 if female) • sCys is serum cystatin C. • min is the minimum of sCys/0.8 or 1. • max indicates the maximum of sCys/0.8 or 1.
CKD-EPI creatinine-cystatin C equation (2012)	$eGFRCr\text{-}Cys = 135 \times \min(sCr/\kappa, 1)\alpha \times \max(sCr/\kappa, 1) - 0.601 \times \min(sCys/0.8, 1) - 0.375 \times \max(sCys/0.8, 1) - 0.711 \times 0.995^{age}$ ($\times$ 0.969 if female) ($\times$ 1.08 if black) • κ is 0.7 for females and 0.9 for males. • α is –0.248 for females and –0.207 for males. • min indicates the minimum of sCr/κ or 1. • max indicates the maximum of sCr/κ or 1.

Alb, Albumin; CrCl, creatinine clearance in mL/min; IBW, ideal body weight (kg); LM, lean mass; sCr, serum or plasma creatinine (mg/dL). For SI conversion purposes, serum or plasma creatinine is converted from μmol/L to mg/dL by multiplying by 0.0113; conversion from creatinine clearance conventional units of mL/min to SI units of mL/s requires multiplication by 0.0167

Equations compiled from references 95-107.

exogenous substances; however, the administration of exogenous substances is not practical for routine individual drug dose calculations in clinical practice because the procedures are not timely and not uniformly available.

Although GFR has been estimated based on the measured urinary clearance of creatinine (mCrCl) derived from a 24-hour urine collection, estimated creatinine clearance (eCrCl) or estimated GFR (eGFR; Table 64.5) are the means predominantly determined in clinical practice from the serum creatinine (sCr) and/or cystatin C (CysC) concentrations and patient factors.[95-101] The advantage of these methods are that timely results are available for routine clinical practice and that for most people, they provide an acceptable assessment of measured GFR (mGFR) or mCrCl, respectively. The variation in sCr assays led to differences in reported serum creatinine values among as well as within laboratories.[102] To address this issue, in 2005, the National Institute of Standards and Technologies released materials that are traceable to the certified reference materials for creatinine whose value was assigned using isotope dilution mass spectroscopy (IDMS).[96,103] It is now estimated that most laboratories currently report creatinine values traceable to this reference method. The use of IDMS creatinine assays will likely lead to less variation in kidney function estimates and theoretically more consistent drug dosing recommendations across institutions and clinical settings. Estimated GFRs based on current creatinine assays are likely to yield different drug dosage recommendations from those intended by the original study, even if the same estimating equation is used due to this change in analytic methodology. It is not possible or practical to repeat all the PK studies with standardized creatinine-determined eCrCl or eGFR, and therefore it is still reasonable to use drug dosing adjustments that appear in FDA- and European Medicines Agency (EMA)–approved product labeling.

Traditionally, drug dosing was based on estimation of creatinine clearance (eCrCl) using the Cockcroft and Gault (CG) formula.[9,100] For implementation in the chemical laboratory report, the CG equation is not suitable because body weight is usually not available in the electronic health

record. The Modification of Diet in Renal Disease (MDRD) equations, which do not require body weight, were developed from an extensive sample of patients with CKD, all of whom had a measured GFR (i.e., iothalamate clearance) of less than 90 mL/min/1.73 m^2).[98,104] They were initially used by clinical laboratories, although they were only validated for patients with a GFR less than 60 mL/min. Therefore, the new CKD-EPI equation was developed to allow estimation of GFR throughout the full range of the chronic kidney disease.[99] The CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) eGFR equation has recently replaced the MDRD equation as the primary index for the staging of CKD, and values are now reported throughout the GFR range by Quest and LabCorp, the two largest laboratory service providers in the United States. For classifying kidney function into one of the five stages of chronic kidney disease, the standardized CKD-EPI formula is currently preferred.[105] Both the MDRD and CKD-EPI equations estimate the GFR for a standard 1.73 m^2 body surface area (BSA); thus, for an individual patient, the BSA must be determined separately so that the eGFR can be expressed in milliliters per minute (mL/min).

Serum cystatin C has been proposed as an alternative marker to estimate GFR, rather than serum creatinine. Multiple equations have been proposed to estimate GFR from age, weight, gender, race, and muscle mass based on serum cystatin C measurements.[106] The combined use of both serum markers, cystatin C and creatinine, allows an even more accurate estimate of kidney function than either of them alone.[107] Adjusting drug doses based on the measurement of cystatin C appears to be an effective and valid tool in the limited number of applications (mainly relating to chemotherapy and antibiotic dosing) for which it has been studied.[108-111]

Few studies have examined the role of alternative GFR estimating equations on drug dosing. In general, when considered against chromium-EDTA measurement of GFR, the MDRD formula tends to underestimate GFR relative to the CG formula.[112-115] Gill and colleagues[114] demonstrated that in a multiethnic and older CKD population, these equations were not interchangeable for the calculation of drug dosing. Discordance between the CG and MDRD equations occurred in 60% of older patients. When MDRD was used instead of CG, 20% fewer patients qualified for a reduction in the dose of amantadine, potentially resulting in an inappropriately high cumulative dose.[114]

PEDIATRICS

The original equation to estimate GFR, as described by Schwartz and colleagues,[116] is dependent on the child's age and length:

$$\text{GFR} = (\text{length [cm]} \times k)/\text{sCr (in mg/dL)}$$

where k is defined by age group: infant (1 to 52 weeks) = 0.45; child (1 to 13 years) = 0.55; adolescent male = 0.7; and adolescent female = 0.55. The serum creatinine level in µmol/L can be converted to mg/dL by multiplication using 0.0113 as the conversion factor. A newer version of the Schwartz equation[117] was developed from a population of 349 children (age 1-19 years) with mild to moderate CKD enrolled in the Chronic Kidney Disease in Children (CKid) study:

$$\text{GFR} = 0.41 \times (\text{length in cm})/\text{sCr in mg/dL}$$

Lee and associates[118] have recently reported that this new Schwartz equation performed better than the original Schwartz equation for patients with moderate CKD, but was less accurate in patients with mild CKD. In pediatric patients, methods incorporating cystatin C have several advantages for evaluating kidney function.[119] The most recent eGFR equation evaluated in pediatrics includes use of cystatin C, blood urea nitrogen (BUN), serum creatinine level (in mg/dL) and demographic data derived from over 600 pediatric patients enrolled in the CKiD study[120]:

$$\begin{aligned}&\text{eGFR (mL/min/1.73 m}^2\text{)}\\&= 39.8 \times (\text{ht [m]/sCr})^{0.456} \times (1.8/\text{cystatin C})^{0.418}\\&\times (30/\text{BUN})^{0.079} \times 1.076^{\text{male}} \times (\text{ht [m]}/1.4)^{0.179}\end{aligned}$$

This equation had the highest R^2 value (0.863) and highest frequency of values within 30% of iohexol-measured GFR (91.3%) when compared to seven other GFR estimating equations.

ACUTE KIDNEY INJURY

At present, the staging of acute kidney injury is based on sequential measurement of the serum creatinine level and urine output.[121-125] Because the GFR is inferred from the serum creatinine or cystatin C, all estimates of kidney function lag the real-time GFR. Although several methods have been proposed to estimate GFR in this patient population, none have been rigorously evaluated, and their use in clinical practice is extremely limited.[119,126-129] The latest proposed method to estimate GFR in patients with AKI is the kinetic GFR (kinetGFR), which is based on age (years), weight (kg), and serum creatinine (µmol/L) and holds true for increasing and decreasing kidney function.[130]

$$\text{kinetGFR} = \frac{[150 - \text{age(years)}] \bullet \text{weight(kg)}}{\text{Cr}_2\text{(µmol/L)}} \bullet \left[1 - \frac{\text{Cr}_2 - \text{Cr}_1}{t_2 - t_1} \bullet \frac{24\text{(hours)}}{200\text{(µmol/L)}}\right]$$

This approach is based on an estimate of the creatinine production similar to the CG equation.[95] The kinetic eGFR incorporates changing creatinine values over specified time intervals as well as the actually measured serum creatinine values, similar to the earlier approaches of Jelliffe,[127] Brater,[126] and Chiou and Hsu.[128] It relates the increase in serum creatinine within a specified time interval to the maximum increase in creatinine level in 1 day. Because creatinine excretion in the urine corresponds to creatinine production, the maximum increase in sCr is about 200 µmol/L if the patient's actual GFR is 0. Thus, the kinetic eGFR predicts what subsequently will be measurable but in fact is already the case with kidney function. The

kinetic eGFR solves the problem that there is always a delay between rapidly changing kidney function and measurable variables, namely sCr or urine output. The calculation of a patient's kinetic eGFR may allow one to use the eCrCl- or eGFR-based dose adjustment recommendations derived from patients with CKD and applicable in part for those with AKI.[130] Rigorous independent studies will be needed to confirm its validity and utility in clinical practice.

PATIENTS RECEIVING DIALYSIS

Some patients on dialysis or on continuous renal replacement therapy (CRRT) have residual kidney function that substantially contributes to the elimination of drugs and their metabolites. Unfortunately, estimating residual kidney function in patients undergoing dialysis is challenging because the serum creatinine concentration reflects not only residual kidney function, but also the efficiency of dialysis and role of muscle mass on creatinine generation. Creatinine clearance measurements are less reliable as a measure of GFR in patients on hemodialysis (HD) or CRRT than in those with earlier stages of CKD because of the following: (1) the volume of urine output is heavily influenced by changing hydration status during the cyclic changes that are inherent as a result of intermittent ultrafiltration; (2) the serum creatinine concentration changes over the duration of the clearance measurement; and (3) tubular secretion of creatinine contributes to its clearance. Estimation of residual kidney function in patients on HD or CRRT is often done by calculating the mean of a measured urea and creatinine clearance. Measuring the elimination of iohexol after an IV dose has been reported to be an accurate and safe measure of residual kidney function in patients on dialysis and can inform drug dosing.[131]

Which one of the many eCrCl or eGFR equations should be used to determine the degree of adjustment of drug dosage regimens for patients with AKI or CKD? The pros and cons of the various GFR estimating equations have been extensively reviewed.[112-115] Moreover, there is a body of evidence on drug dosing methodology that has been derived based on measured creatinine clearance or eCrCl using the CG equation.[132] The MDRD and CKD-EPI equations significantly overestimated CrCl (mCrCl and CG) in older individuals.[114] This has led to dose calculation errors for many drugs, particularly in individuals with severe CKD. Thus, we have concluded that eGFR equations should not be substituted in place of the CG equation in older adults for the purpose of renal dosage adjustments.

It is the advantage of the CG equation that body weight is considered as a determinant of drug distribution volume. The choice of the optimal GFR estimating equation is of utmost importance for drugs with a narrow therapeutic index for which dosing individualization is often continuous rather than categoric. Finally, because most pharmacokinetic studies in patients with CKD conducted over the last 40 years have used estimated or measured CrCl as the estimate of GFR, the CG method in adults and the latest Schwartz method in children remain the criteria to be used. However, for patients with AKI, there is no obvious best choice for GFR estimation to guide drug dosing.

DRUG DOSING CONSIDERATIONS

PATIENTS WITH CHRONIC KIDNEY DISEASE

Despite the availability of numerous guidelines regarding drug dosing for patients with impaired kidney function, there is insufficient evidence as to which, if any, is preferred.[5,13,35,133-135] Occasionally, recommendations derived from postmarketing studies conflict with the information in these reports, as well as the official FDA or EMA product labeling. Prior to 1998, there were no official guidelines regarding when and how to characterize the relationship between the pharmacokinetics and pharmacodynamics of a drug and kidney function. The FDA guidelines issued in May 1998[136] and the 2010 proposed revision,[137] and the EMA guidelines of 2004,[138] have provided frameworks for which drugs should be evaluated and guidance regarding study design, data analysis, interpretation of study results, and recommendations for the incorporation of data into product labeling.

GOALS OF THERAPY

The desired goal is typically the maintenance of a similar peak, trough, or average steady-state drug concentration or, for antibiotics, an optimized pharmacodynamic measure, such as the time above the MIC or the ratio of the drug area under the AUC to the MIC, as would be optimal for persons with normal kidney function[8,86,139] (see earlier, "Pharmacodynamics," for more detail). When there is a significant relationship between drug concentration and clinical response[86] (e.g., aminoglycosides) or toxicity[39] (e.g., phenytoin), attainment of the specific target values becomes critical. If, however, no specific PK or PD target values have been reported, a regimen goal of attaining and maintaining the same average steady-state concentration may be appropriate.

INDIVIDUALIZATION OF THE DRUG DOSAGE REGIMEN

Most dosage adjustment guidelines have proposed the use of a fixed dose or interval for patients with broad ranges of kidney function.[35,134,135,140-143] The mild, moderate, and severe CKD categories vary among reference sources, so the recommended regimen may not be optimal for all patients whose kidney function lies within the range, especially for agents with a narrow therapeutic index.[9] The approach to developing drug dosage adjustment recommendations for the patient with CKD is predicated on attainment of the desired exposure goal at steady state. To achieve the desired goal in a timely fashion, a stepwise approach that includes multiple considerations (Table 64.6) for each individual drug should be considered.[135] The following considerations may help guide individualization of therapy.

The initial or loading dose (LD), which in many patients with AKI will be larger than the typical maintenance dose, should be calculated to achieve the desired C_{max} therapeutic drug concentration. An LD should be used for most patients with stage 4 or 5 CKD to achieve the desired steady-state concentration rapidly and in which the volume of distribution (V_D) of a drug is significantly increased in patients with AKI and CKD relative to those with normal kidney function.

Table 64.6 Stepwise Approach to Adjust Drug Dosage Regimens for Patients with Impaired Kidney Function

Step	Process	Assessment
1	Obtain history and relevant demographic and clinical information.	Record demographic information, obtain past medical history. including history of renal disease, and record current laboratory information (e.g., serum creatinine).
2	Estimate creatinine clearance.	Use Cockcroft-Gault equation to estimate creatinine clearance, or calculate creatinine clearance from timed urine collection.
3	Review current medications.	Identify drugs for which individualization of the treatment regimen will be necessary
4	Calculate individualized treatment regimen.	Determine treatment goals (see text); calculate dosage regimen based on pharmacokinetic characteristics of the drug and patient's renal function.
5	Monitor.	Monitor parameters of drug response and toxicity; monitor drug levels if available or applicable.
6	Revise regimen.	Adjust regimen based on drug response or change in patient status (including renal function), as warranted.

Adapted from Mohammad RA, Matzke GR. Drug dosing in renal failure. In DiPiro J, Talbert R, Yee G, et al, editors: Pharmacotherapy: a pathophysiologic approach, *ed 9, New York, 2014, McGraw-Hill.*

If the relationship between V_D and CrCl has been characterized, then the V_D should be estimated from that relationship. If no LD is prescribed, four half-lives of the drug must pass before the desired steady-state plasma concentration is achieved; however, doing so may contribute to therapeutic failure. The proportion of the LD given affects the magnitude of the steady-state plasma concentration and how rapidly plasma concentrations are achieved. An LD equivalent to the dose given to a patient with normal kidney function should be given to patients with impaired kidney function if the drug's half-life is especially long and if the physical examination suggests normal ECF volume. If the patient has marked volume expansion or evidence indicates that the V_D of the drug is larger in patients with CKD, then a higher dose can be calculated from the following expression:

$$LD = V_D \times C_{max} \times IBW$$

where V_D is the drug's volume of distribution (in liters per kilogram of IBW in those with CKD), IBW is the patient's ideal body weight (in kilograms), and C_{max} is the desired steady-state maximum plasma drug concentration.

The primary reference for information regarding the maintenance dose for patients with CKD should be the FDA and/or EMA official product labeling. If no official drug dosing guidance is available, one may need to search the literature to find a recommendation strategy derived from nonregulatory or postmarketing clinical investigations. If no such resource is found, one can consult online or published tertiary references that have developed dosing recommendations based on the Dettli or Tozer method, initially published in 1974.[11,12] They used similar foundational PK characteristics and approaches to calculate the maintenance dose for a patient with a given eCrCl. In essence, either the dose (D) should be reduced or the interval (τ) extended. When the dose is reduced, the C_{max} will be lower and the trough concentrations will be higher than those observed in persons with normal kidney function. When the administration interval is extended, the peak and trough concentrations are kept constant but the dosing frequency decreases (see Figure 64.4).

To maintain the normal dose interval in patients with impaired kidney function, the amount of each dose after the loading dose can be estimated from the following equation:

$$D_f = D_n \times Q$$

where D_f is the dose for the patient with impaired kidney function to be given at the normal dosing interval, D_n is the normal dose, and Q is the dosage adjustment factor. The dosage adjustment factor (Q) can be calculated as:

$$Q = 1 - (f_e[1 - KF])$$

where f_e is the fraction of the drug eliminated unchanged renally in a patient with normal renal function, KF is the ratio of the patient's CrCl or GFR to the assumed normal value of 120 mL/min (equivalent to 2.00 mL/sec). Thus, for a drug that is 85% eliminated unchanged by the kidneys, the Q factor in a patient who has a CrCl of 10 mL/min (0.17 mL/sec) would be as follows:

$$\begin{aligned} Q &= 1 - (0.85[1 - {}^{10}/_{120}]) \\ &= 1 - (0.85[0.92]) \\ &= 1 - 0.78 \\ &= 0.22 \end{aligned}$$

If one desires to give the same maintenance dose, a factor that may be required because of the limited availability of alternative formulations, the dosing interval at which the normal dose should be administered can be calculated as follows:

$$\tau_f = \tau_n / Q$$

The decision to extend the dosing interval beyond a 24-hour period should be based on the need to maintain therapeutic peak or trough levels. The dosing interval may be prolonged if the peak level is most important. Prolonging

the dose interval in patients on dialysis is frequently a convenient method to modify the drug dosage regimen. This method is particularly useful for drugs with a long plasma half-life. In general, drugs removed by dialysis given once daily should be given after the dialysis treatment, with aminoglycosides a notable exception.[144-146]

A third alternative that is especially helpful when the calculated dose or dosing interval is impractical is to select the administration interval according to the target trough concentration while the peak is kept constant:

$$\tau_{target} = \left(t_{1/2}/0.693\right) \times \ln\left(C_{peak}/C_{trough\text{-}target}\right)$$

$$D = LD \times \left(1 - C_{trough\text{-}target}/C_{peak}\right)$$

Alternatively, one can calculate the adjusted dose (D_p) to be given at the predetermined practical dosage interval (τ_p or $\tau_{ptarget}$) as follows:

$$D_p = (D_n \times \tau_p \times Q)/\tau_n$$

where τ_f is the estimated dosing interval, as calculated from the above equation for $\tau_{ptarget}$, or the clinically practical value for the renally impaired patient (e.g., 12, 18, 24, 36, 48 hours). These approaches, which use a combination of the dose reduction and interval prolongation methods, are often the most clinically practical. When in doubt, clinicians should consult an experienced pharmacist, preferably one with extensive experience in evaluating patients with CKD and altered body composition (e.g., fluid overload).

MEASUREMENT OF THERAPEUTIC DRUG LEVELS

Measuring drug concentrations is one way to optimize therapeutic regimens and account for changes among and within individuals. Therapeutic drug monitoring requires availability of rapid, specific, and reliable assays and known correlations of drug concentration to therapeutic and toxic outcomes. Hypoalbuminemia may influence interpretation of drug concentrations because the total drug concentration may be reduced, even when the active unbound drug concentration generally is not. Unbound drug concentrations are often not clinically available, so clinicians must empirically consider the influence of hypoalbuminemia in their interpretation of measured total drug concentrations, as in the case of phenytoin and several antibiotics (e.g., daptomycin).[39,147,148]

PATIENTS WITH ACUTE KIDNEY INJURY

Critically ill patients frequently develop AKI; depending on the definition, from 5% to 15% of all non–same-day hospitalization care is complicated by AKI.[25,149] In most cases, drug dosing is based on drug disposition information derived from studies in stable patients with CKD. Unfortunately, there are large gaps in knowledge of drug metabolism and disposition in patients with AKI; thus, patients may be at significant risk for underdosing as well as overdosing. More than 30 definitions of AKI have been published in the literature.[121-125] The lack of a consensus definition and classification of AKI reflects the wide range of causes and severity with which it presents. The presentation can vary from part of multiorgan dysfunction in critically ill patients to isolated AKI.[150] As a result, AKI-related, in-hospital mortality rates vary from 70% in intensive care unit (ICU) patients[151] to 35% in other hospitalized patients.[152]

The potential effects of AKI on drug dosing are of major consequence because AKI patients are often critically ill and require multiple drug therapies, some of which may be nephrotoxic or require dose modification in the setting of AKI. The pharmacokinetic changes in absorption, distribution, metabolism, and excretion presented earlier in this chapter and in other sources are foundational to optimal patient care.[26,153] The clinician needs to appreciate these factors and realize that they may worsen and improve over the period of evolution or recovery of the AKI episode. Critically ill patients with AKI typically have minimal oral intake of food and liquids and commonly require parenteral administration of drugs otherwise given orally (e.g., antihypertensives, immunosuppressives).

There is a paucity of dosing algorithms to guide pharmacotherapy, derived from investigations of the PK and PD of medications in patients with AKI. Most of the critical care literature and almost all FDA or EMA product labeling contain drug dosage recommendations derived from observations of patients with CKD and ESKD. The limited data available in the setting of AKI have predominantly been developed by clinicians; rarely is this information incorporated into official product labeling. The principles of drug dosage regimen modification described earlier for use in CKD thus remain the foundation for therapy optimization in patients with AKI.

LOADING DOSE

Many patients with AKI are overhydrated, and the distribution volume is much larger than under normal conditions. Thus, the LD may need to be higher than the normal starting dose for persons with normal kidney function. Because the V_D of many drugs, especially hydrophilic antibiotics, including β-lactams, cephalosporins, and carbapenems, are significantly increased in the presence of AKI, the administration of proactive loading doses (25% > normal) are highly recommended.

MAINTENANCE DOSE

Forecasting the degree and rate of change in kidney function and fluid volume status is extremely challenging. Thus, maintenance dosing regimens for many drugs, especially antimicrobial agents, should be initiated at normal or near-normal dosage regimens and adjustments made based on the relationship between drug pharmacokinetic characteristics and kidney function, as described earlier. Prospective measurement of serum drug concentrations and analysis using state of the art PK and PD approaches should be used whenever possible.

PATIENTS UNDERGOING HEMODIALYSIS

The optimization of pharmacotherapy for patients receiving maintenance hemodialysis and emergent hemodialysis are both critically dependent on the availability of reliable information from well-designed pharmacokinetic studies.[154-157] The impact of hemodialysis on drug therapy is dependent on the drug characteristics and dialysis prescription. Drug-related factors include molecular weight (MW)

or size, degree of protein binding, and distribution volume.[135] The vast majority of hemodialysis filters in use up until the mid-1990s were generally impermeable to drugs with a molecular weight greater than 1 kDa.[155-157] Dialysis membranes in the twenty-first century are predominantly composed of semisynthetic or synthetic materials, which have larger pore sizes, and this allows the ready passage of drugs that have a MW up to 20 kDa.

Drug clearance during dialysis can occur by three different processes.[6,156,157] Drug removal by conventional HD occurs primarily by diffusion down a concentration gradient from the plasma to the dialysate. Removal of low-MW drugs is enhanced by increasing blood and dialysate flow rates and by using large surface area dialyzers. Larger molecules require more porous membranes for increased removal. The clearance of a drug by conventional HD can be estimated from the unbound fraction (f_u) and the following relationship:

$$Cl_{HD} = f_u \times Cl_{urea} \times (60/MW_{drug})$$

where Cl_{HD} is the drug's clearance by HD, Cl_{urea} is the dialyzer clearance of urea, and MW_{drug} is the MW of the drug. The urea clearance for most conventional dialyzers varies between 150 and 200 mL/min and is markedly less than values reported with high-flux hemodialyzers.[157] With high-flux hemodialysis, the volume of distribution and degree of protein binding of the drug become more important determinants of dialyzer clearance. The hemodialyzer clearance of drugs that are not highly protein-bound and have relatively small volumes of distribution runs in parallel to urea clearance, despite their large molecular mass.[158-160] The convective transport and removal of drugs during high-flux HD depends primarily on filtration pressure gradient, treatment time, blood, and dialysate flow rates. Despite the widespread adoption of high-flux hemodialysis in certain parts of the world, there are sparse quantitative data on drug clearance.

Small solute removal is more efficient if the frequency of hemodialysis is increased. Daily and nocturnal dialysis therapies yield different clearance values compared with thrice-weekly, high-flux, in-center hemodialysis, and also differ from each other. There has been very little investigation of the effects of frequent or more intensive hemodialysis regimens on drug disposition or comparison among modalities. As a result, drug dosing in patients should be guided by drug level monitoring when possible. One of the few studies to investigate drug clearance by one of these variants focused on the aminoglycoside antibiotic gentamicin. Slow nocturnal dialysis required a significant increase in gentamicin dosage to achieve therapeutic levels compared with conventional thrice-weekly dialysis.[161] The variability in drug clearance was high and did not correlate with small solute clearance. Drugs with a molecular size of 500 to 5000 Da appear to be particularly likely to have an increased clearance with this modality. Studies of modeled clearance have suggested that frequent hemodialysis regimens would be associated with enhanced clearance (and the potential of underdosing) of daptomycin.[147,148,162,163] This enhanced clearance was confirmed in the setting of AKI when the PK associated with extended daily dialysis were investigated. These findings should be transferable to maintenance HD, with a degree of caution about the effects on distribution volumes that might arise in the setting of acute septic shock.[164,147] One of the other effects of prolonged HD appears to be a reduction in rebound of drug concentrations after the termination of dialysis.[165,166] This is probably because the rate of transfer from the peripheral to central compartment relative to the rate of diffusive removal is lower.

There were more than 100 different dialysis or hemofilters available in the United States in 2013, and at least four distinct variants of hemodialysis are currently being used.[6] The effect of hemodialysis or hemofiltration on the disposition of a drug may vary markedly and, because dialyzer or hemofilter clearance is rarely evaluated more than once, clinicians have to extrapolate data from one procedure to another.[167,168] The enhanced efficiency of twenty-first century dialyzers means that most of the literature for medications developed prior to 2000 probably reflects an underestimation of the impact of hemodialysis.[1,155] Consequently, the dosage may need to be empirically increased by 25% to 50%. Therapeutic drug monitoring should be used for drugs with narrow therapeutic indices to optimize safety and efficacy.

ASSESSMENT OF THE IMPACT OF HEMODIALYSIS

The most commonly used means for assessing the effect of hemodialysis is to calculate the dialyzer clearance of a drug (Cl^p_D) from plasma, as follows:

$$Cl^p_D = Q_p([A_p - V_p]/A_p)$$

where Q_p is plasma flow through the dialyzer, A_p is the concentration of drug in plasma going into the dialyzer, and V_p is the plasma concentration of drug leaving the dialyzer.[135,166] This equation tends to underestimate hemodialysis clearance for drugs that readily partition into and out of erythrocytes. In addition, venous plasma concentrations may be artificially high if extensive ultrafiltration is performed, so thus Cl^p_D will be lower than it really is. Because of these limitations, the recovery clearance approach remains the benchmark for the determination of dialyzer clearance and can be calculated as follows[135]:

$$Cl^r_D = R/AUC_{0\text{-}t}$$

where R is the total amount of drug recovered unchanged in the dialysate and $AUC_{0\text{-}t}$ is the area under the predialyzer plasma concentration-time curve during the period of time that the dialysate was collected. The hemodialysis clearance values reported in the literature may vary significantly, depending on which of these methods were used.[135,156]

It is common practice in most hemodialysis units to administer drugs after dialysis to minimize the loss of drug that would result from the additional clearance during hemodialysis. However, performing hemodialysis immediately after dosing might be a good option for removal of toxic antibiotics[139,144-146,164,169] and high-dose, anticancer therapy. For anticancer drugs, the predialysis administration of a normal dose makes sense when the patient undergoes hemodialysis 2 to 12 hours later. This strategy delivers the desired maximum plasma concentration effect while minimizing the toxic drug or metabolic effects[170-183] (Table

64.7). Emerging PK and PD considerations suggest that administration after hemodialysis may not be the optimal approach for several other agents, such as aminoglycosides and vancomycin.[139,144-146,164,169] High-bolus dosing immediately before or during the last hour of dialysis has been proposed for some antibiotics, but there have been few clinical studies.

If the drug is given after dialysis, the postdialysis dose (D_{HD}) should first replace the amount eliminated during the interval between dialysis sessions (D_{fail}) that is the result of clearance by the patient's residual renal function and nonrenal clearance. Also, the fraction of drug removed by hemodialysis (FR) should be estimated and a supplementary dose calculated (D_{suppl}). The dose the patient should receive after HD would thus be the sum of these two doses (Figure 64.5):

$$D_{HD} = D_{fail} + D_{suppl} = D_{fail} + (FR \times (D_{start} - F_{fail})$$

PATIENTS RECEIVING CONTINUOUS RENAL REPLACEMENT THERAPY

CRRT and hybrid RRTs are commonly used to manage patients with AKI in ICUs.[184] CRRT seems to provide less of a challenge for drug dosing than intermittent HD because its continuous nature is analogous with drug removal by native kidneys and potentially amenable to the use of standard, first-order drug clearance equations to calculate dosing. However, in practice, CRRT rarely proves as continuous as planned. The CRRT modality and details of the therapy prescription can also have significant effects on drug clearance. MW, membrane characteristics (highly variable between systems), blood flow rate, and dialysate flow rate determine the rate and extent of drug removal.[185-189] Because most drugs are less than 1.5 kDa, drug removal by CRRT does not depend greatly on MW. The use of higher hemofiltration volumes, especially if infused prefilter, can also affect clearance. The removal of urea, creatinine, and vancomycin were increased by 15% to 25% by the predilution modality.[190-192]

CRRT clearances have been noted to decline because the time the hemofilter has been in use increases due to the accumulation of protein on the dialysis membrane. Clotting within the hemofilter's hollow fibers also reduces the overall surface area for clearance. Although these factors have received little direct investigation, it appears that they do affect drug clearance.[192]

Drug protein binding also affects how much is removed during CRRT because only unbound drug is available for elimination by CRRT. Protein binding of more than 80% provides a substantial barrier to drug removal by convection or diffusion. During continuous venovenous hemofiltration,

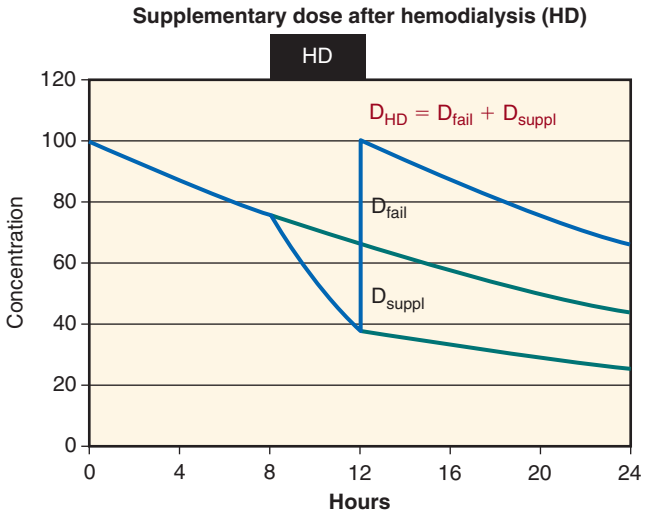

Figure 64.5 To maintain therapeutic target concentrations, a supplementary dose must be given after hemodialysis to replace the removed fraction of the dose. The dose after dialysis (D_{HD}) combines both, the adjusted maintenance dose (D_{fail}) and supplementary dose (D_{suppl}).

Table 64.7 Drugs Best Administered Prior to Hemodialysis

Drug Class	Examples	Drug Fraction Removed by One Dialysis Session (FR)	Reference
Anticancer	Carboplatin	20%	Chatelut et al[170]; Kamata et al[171]; Yoshida et al[172]; Oguri et al[173]
	Cisplatin	85%	Watanabe et al[174]
	Oxaliplatin	65%	Katsumata et al[175]
	Cyclophosphamide	22% (M % unknown)	Haubitz et al[176]
	Ifosphamide	70% to 87% (M, 72% to 77%)	Carlson et al[177]
	Capecitabine (FBAL)	50%	Walko and Lindley[178]
	Gemcitabine (dFdU)	50%	Koolen et al[179]
	Methotrexate	36%	Garlich and Goldfarb[180]
	Cytosine arabinoside	39% (M, 52% to 63%)	Radeski et al[181]
	Topotecan	50%	Herrington et al[182]
Aminoglycoside	Gentamicin	75%	Veinstein et al[164]
	Tobramicin	80%	Kamel et al[146]
Contrast agent	Gadolinium	65% to 74%	Rodby[183]

M, Metabolite.

drug clearance generally approximates the ultrafiltration rate. The addition of diffusion by continuous venovenous hemodiafiltration increases drug clearance and is dependent on the ultrafiltration and dialysate flow rates. As is the case during high-flux dialysis, drug removal often parallels the removal of urea and creatinine. Thus, the simplest method for estimating drug removal during CRRT is to estimate urea or creatinine clearance.[8,154,190-192]

Hybrid RRTs, including sustained or slow low-efficiency dialysis (SLED), extended daily dialysis (EDD), continuous SLED (c-SLED), slow low-efficiency daily dialysis (SLEDD), and slow low-efficiency daily hemodiafiltration (SLEDD-f), which use higher dialysate flow rates and shorter treatment periods (6 to 12 hours in duration), are frequently used as well.[193-198] To date, hybrid RRT pharmacokinetic data have been published for fewer than 20 drugs.[1] The improvement of RRT machines and filters has rendered old dosing guidelines for drugs, especially antibiotics, obsolete and potentially hazardous. Although there are only a few FDA or EMA official drug dosing recommendations for patients receiving CRRT, several published dosing guidelines are widely used.[8,168,190-192] Unfortunately, these recommendations have generally not been prospectively evaluated, and their influence on patient outcomes is largely unknown.

In the absence of FDA or EMA recommendations, tertiary reference sources, or any published studies relating to the handling of a drug by CRRT (common with agents that are new to the market), may be necessary for the clinician to formulate a dosing regimen using the PK principles presented in this chapter. If the volume of distribution is large (>1 L/kg), there is a low likelihood that CRRT will substantially remove it. The use of a high-flux dialyzer or hemofilter allows for drugs with a MW below 20 kDa to be readily removed. If the clearance of the drug by CRRT or hybrid RRT is less than 25% of the patient's estimated total body clearance, a dosing adjustment is probably unnecessary. On the other hand, if CRRT or hybrid RRT results in an augmentation of drug clearance by 25% to 50%, an LD based on the patient's estimated volume status should be given, and maintenance doses similar to that given to a patient with a CrCl of 30 to 50 mL/min can be used. Such estimates obviously have to take into account changing volume status and be supplemented by regular drug concentration measurements, if technically feasible.

PATIENTS UNDERGOING PERITONEAL DIALYSIS

Peritoneal dialysis, as practiced in 2014, is very unlikely to enhance total body clearance of any drug by more than 10 mL/min because most typical peritoneal dialysis prescriptions can achieve a urea clearance of about 10 mL/min or lower. Because most drugs are larger than urea, their clearance is even less; thus, it is very likely to be from 5 to 7.5 mL/min or less. Many studies performed in the 1970s and 1980s showed that drug clearances by peritoneal dialysis were in this very low range, so one can conclude that peritoneal dialysis does not enhance drug removal to a degree that would require a special dosage regimen modification.[199-202] Thus, oral or IV drug therapy recommendations for patients with an eCrCl or eGFR less than 15 mL/min are likely clinically useful.

Intraperitoneal drug administration is well accepted for the treatment of peritoneal dialysis–associated peritonitis and other infections.[203-205] Administration intervals depend on the half-life of the drug, which is mainly determined by residual renal and extrarenal metabolic clearance. Long-standing experience with intermittent antibiotic administration exists for the glycopeptides vancomycin and teicoplanin, which can be administered at 5- to 7-day intervals, as well as for aminoglycosides and cephalosporins, which are suitable for once-daily dosing.[204,206]

Patients treated by automated peritoneal dialysis (APD), with frequent short-dialysis cycles, may achieve higher plasma concentrations as compared to antibiotic loading in a single extended dwell period in patients on continuous ambulatory peritoneal dialysis (CAPD). Conversely, the higher dialysate flow and small-molecule clearance achieved with APD regimens may lead to a greater peritoneal clearance of antibiotic in the intervals between dosing.[204]

Because most pharmacokinetic studies establishing peritoneal antibiotic doses have used 4- to 8-hour loading periods, it is recommended to perform antibiotic loading by an extended cycle both in CAPD and APD patients. For intermittent maintenance dosing, a long nighttime dwell time should be used in CAPD patients and a long daytime dwell time in APD patients. In clinical practice, intraperitoneal antibiotic dosing has not been unequivocally successful in eradicating bacterial growth, partially questioning the concept of antibiotic back diffusion into the peritoneal cavity.

CLINICAL BOTTOM LINE

Recommendations for dosing selected drugs in patients with CKD and AKI are given in Table 64.8. These are meant only as a guide and do not imply the safety or efficacy of a recommended dose in an individual patient. A loading dose equivalent to the usual dose in patients with normal kidney function should be considered for drugs with half-lives longer than 12 hours. No controlled clinical trials have established the efficacy of these dosage recommendations. The effect on drug removal of HD, ambulatory peritoneal dialysis, and CRRT is variable and the values in the table are more qualitative than quantitative. Most of these recommendations were established before high-efficiency HD treatments were practical, continuous cycling nocturnal peritoneal dialysis was common, and diffusion was added to hemofiltration in CRRT.

Complete reference list available at ExpertConsult.com.

Table 64.8 Recommendations for Dosing Selected Drugs in Patients with Chronic Kidney Disease or Acute Kidney Injury

	Degree of Drug Dose Reduction or Interval Prolongation			Dosage Recommendations for Patients Receiving Renal Replacement Therapy		
Drug	GFR > 50 mL/min	GFR = 10-50 mL/min	GFR < 10 mL/min	HD	CAPD	CRRT
Acebutolol	100%	50%	25%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Acetaminophen	q4h	q6h	q8h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Acetazolamide	q6h	q12h	q24h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Acetohexamide	Avoid	Avoid	Avoid	Avoid	Avoid	Avoid
Acetohydroxamic acid	100%	100%	Avoid	Unknown	Unknown	Unknown
Acetylsalicylic acid	q4h	q4-6h	Avoid	As normal GFR	As normal GFR	Dose as GFR 10-50
Acrivastine	8 mg q6h	8 mg q8-12h	8 mg q12-24h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Acyclovir	5 mg/kg q8h	5 mg/kg q12-24h	2.5-5 mg/kg q24h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Allopurinol	100%	50%	33%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Amantadine	q24h	q48-72h	q7days	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Amikacin*	5-6 mg/kg q12h	3-4 mg/kg q24h	2 mg/kg q24-48h	5 mg/kg after HD	15-20 mg/L/day	7.5 mg/kg q24h
Amiloride	100%	50%	Avoid	NA	NA	NA
Amoxapine	100%	100%	100%	Unknown	Unknown	Dose as GFR 10-50
Amphotericin	q24h	q24h	q24h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Amphotericin B	q24h	q24h	q24h	Dose as GFR < 10	Dose as GFR < 10	Dose for GFR 10-50
Amphotericin B lipid	q24h	q24h	q24h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Ampicillin	250 mg-2 g q4-6h	250 mg-2 g q6h	250 mg-1 g q6h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Atenolol	100% q24h	50% q24h	25% q24h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Auranofin	6 mg q24h	3 mg q24h	Avoid	Avoid	Avoid	Dose as GFR 10-50
Azathioprine	100%	75%-100%	50%-100%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Aztreonam	100%	50%	25%	Dose as GFR < 10	Dose for GFR < 10	Dose as GFR 10-50
Benazepril	100%	50%-75%	25%-50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Bezafibrate	50%-100%	25%-50%	Avoid	200 mg q72h	200 mg q72h	200 mg q24-48h
Bisoprolol	100%	100%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Bleomycin	100%	75%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Bretylium	100%	25%-50%	25%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Bupropion	100% q24h	100% q24h	100% q24h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Butorphanol	100%	75%	50%	Unknown	Unknown	Dose as GFR 10-50
Capreomycin	q24h	q24h	q48h	Dose as GFR < 10	Dose as GFR < 10	As normal GFR
Captopril	100% q8-12h	75% q12-18h	50% q24h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Carboplatin	100%	50%	25%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Carteolol	100%	50%	25%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Cefaclor	100%	100%	50%-100%	250-500 mg q8h	250 mg q8-12h	Dose as GFR 10-50
Cefadroxil	q12h	q12h	q24h	0.5-1.0 g after HD	0.5 g/day	Dose as GFR 10-50
Cefamandole	q6h	q6-8h	q8-12h	0.5-1.0 g q12h	0.5-1.0g q12h	Dose as GFR 10-50
Cefazolin	q8h	q12h	50% q24-48h	15-20 mg/kg after HD	Dose as GFR 10-50	Dose as GFR 10-50
Cefepime	q12h	50%-100% q24h	25%-50% q24h	Dose as GFR < 10	Dose for GFR < 10	1-2 g q12h
Cefixime	100%	75%-100%	50%	Dose as GFR < 10	Dose for GFR < 10	Dose as GFR 10-50
Cefotaxime	q6h	q6-12h	1g q8-12h	Dose as GFR < 10	Dose as GFR < 10	1-2 g q12h
Cefotetan	q12h	q24h	q48h	1 g after HD	1 g q24h	Dose as GFR 10-50
Cefoxitin	q6-8h	q8-12h	q24-48h	1 g after HD	1 g q24h	Dose as GFR 10-50
Cefpodoxime	100%	100%	100-200 mg q24-48h	Dose as GFR < 10	Dose as GFR < 10	As normal GFR
Cefprozil	100%	50% q12h	50% q12h	250 mg after HD	Dose as GFR < 10	Dose as GFR < 10
Ceftazidime	100%	1-2 g q24h	0.5-1 g q48h	1 g after HD	0.5-1g q24h	1-2 g q12h
Ceftibuten	100%	50%	25%	400 mg after HD	Dose as GFR < 10	Dose as GFR 10-50

Ceftizoxime	q8h	q12h	q24h	1 g after HD	0.5-1.0 g q24h	Dose as GFR 10-50
Cefuroxime (IV)	100% q8h	q8-12h	750 mg q12h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Celiprolol	100%	100%	75%	Dose as GFR < 10	Dose as GFR < 10	As normal GFR
Cephalexin	250-500 mg q6h	250-500 mg q8-12h	250-500 mg q12-24h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Cephradine	100%	50%	25%	Dose as GFR < 10	Dose for GFR < 10	As normal GFR
Cetirizine	100%	100%	50%	Dose as GFR < 10	Dose as GFR < 10	As normal GFR
Chloroquine	100%	100%	50%	Dose as GFR < 10	Dose as GFR < 10	As normal GFR
Chlorpropamide	50%	Avoid	Avoid	Avoid	Avoid	Avoid
Chlorthalidone	q24h	Avoid	Avoid	Avoid	Avoid	Unknown
Cibenzoline	100% q12h	100% q12h	66% q24h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Cidofovir	50%-100%	Avoid	Avoid	No data	No data	Avoid
Cilazapril	75% q24h	50% q24-48h	10%-25% q72h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Cimetidine	100%	50%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Ciprofloxacin	100%	50%-100%	50%	250 mg q12h	250 mg q8h	200 mg IV q12h
Cisplatin	100%	75%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Clarithromycin	100%	75%	50%-75%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Clodronate	100%	50%	Avoid	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Clofazimine	100%	100%	100%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Clofibrate	q6-12h	q12-18h	Avoid	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Clomipramine	100%	Start at lower dose, monitor effect	Start at lower dose, monitor effect	Dose as GFR 10-50	Dose as GFR 10-50	Dose as GFR 10-50
Clonidine	q12h	q12-24h	q24h	As normal GFR	As normal GFR	As normal GFR
Clopidogrel	100%	100%	100%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Codeine	100%	75%	50%	As normal GFR	As normal GFR	As normal GFR
Colchicine	100%	100%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Cyclophosphamide	100%	75%-100%	50-75%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Cycloserine	q12h	q12-24h	q24h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Dapsone	100%	100%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Daunorubicin	100%	75%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Didanosine	50%-100%	33%-50%	25%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Diflunisal	100%	50%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Digitoxin	100%	100%	50%-75%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Digoxin*	100% q24h	25%-50% q24h	10-25% q24-48h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Disopyramide	q8h	q12h	q48h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Dobutamine	100%	100%	100%	As normal GFR	As normal GFR	As normal GFR
Doxacurium	100%	50%	50%	Unknown	Unknown	Dose as GFR 10-50
Dyphylline	75%	50%	25%	Dose as GFR < 10	Unknown	Dose as GFR 10-50
Emtricitabine	q24h	q48-72h	q96h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Enalapril	100%	50%-100%	25%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Ertapenem	100%	100%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Erythromycin	100%	100%	50%-75%	Dose as GFR < 10	Dose as GFR < 10	As normal GFR
Ethambutol	q24h	q24-36h	q48h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Ethchlorvynol	100%	Avoid	Avoid	Dose as GFR < 10	Dose as GFR < 10	NA
Ethionamide	100%	100%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Ethosuximide	100%	100%	75%-100%	As normal GFR	As normal GFR	As normal GFR
Etoposide	100%	75%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Famciclovir	100%	q12-24h	50% q24-48h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Famotidine	100%	50%	20 mg q24h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Fentanyl	100%	75%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Fexofenadine	q12h	q12-24h	q24h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50

Continued on following page

Table 84.8 Recommendations for Dosing Selected Drugs in Patients with Chronic Kidney Disease or Acute Kidney Injury (Continued)

Drug	Degree of Drug Dose Reduction or Interval Prolongation			Dosage Recommendations for Patients Receiving Renal Replacement Therapy		
	GFR > 50 mL/min	GFR = 10-50 mL/min	GFR < 10 mL/min	HD	CAPD	CRRT
Flecainide	100%	50%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Fluconazole	100%	100%	50%	Dose as GFR < 10	Dose as GFR < 10	As normal GFR
Flucytosine	50 mg/kg q12h	50 mg/kg q24h	50 mg/kg q24-48h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Fludarabine	75%-100%	75%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Foscarnet	28 mg/kg/q8h	15 mg/kg/q8h	6 mg/kg/q8h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Fosinopril	100%	100%	75%-100%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Gabapentin	400 mg q8h	300 mg q12-24h	300 mg q48h	As normal GFR	As normal GFR	As normal GFR
Gallamine	75%	Avoid	Avoid	NA	NA	Avoid
Ganciclovir	2.5-5 mg/kg q12h	1.25-2.5 mg/kg q24h	1.25 mg/kg q24h	Dose as GFR < 10	Dose as GFR < 10	2.5 mg/kg q24h
Gemfibrozil	100%	75%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Gentamicin*	5-7 mg/kg/day	2-3 mg/kg/day by levels	2 mg/kg q48-72h by levels	3 mg/kg after HD by levels	3-4 mg/L/day by levels	Dose as GFR 10-50
Gliclazide	50%-100%	20-40 mg/day	20-40 mg/day	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Glipizide	100%	50%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR < 10
Guanadrel	q12h	q12-24h	q24-48h	Unknown	Unknown	Dose as GFR 10-50
Guanethidine	q24h	q24h	q24-36h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Hydralazine	q8h	q8h	q8-12h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Hydroxyurea	100%	50%	20%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Hydroxyzine	100%	50%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Idarubicin	100%	75%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Ifosfamide	100%	75%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Iloprost	100%	100%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Imipenem	100%	50%	25%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Indapamide	100%	100%	50%	Dose as GFR < 10	Dose as GFR < 10	NA
Indobufen	100%	50%	25%	Unknown	Unknown	Unknown
Isoniazid	100%	100%	75%-100%	Dose as GFR < 10	Dose as GFR < 10	As normal GFR
Kanamycin*	7.5 mg/kg q12h	7.5 mg/kg q24-72h	7.5 mg/kg q48-72h	50% the normal dose	15-20 mg/L/day	Dose as GFR 10-50
Ketorolac	100%	50%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Lamivudine	100%	50-150 mg q24h	25-50 mg q24h	Dose as GFR < 10	Dose as GFR < 10	50 mg q24h
Lepirudin	100%	25%-50%	Avoid	Avoid	Avoid	Avoid
Levofloxacin	100%	50%	25%-50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Lincomycin	q6h	q6-12h	q12-24h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Lisinopril	100%	50%-75%	25%-50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Lithium carbonate*	100%	50%-75%	25%-50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Lomefloxacin	100%	50%-100%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Loracarbef	q12h	q24h	q3-5days	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Melphalan	100%	75%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Meperidine	100%	75%	50%	Avoid	Avoid	Avoid
Meprobamate	q6h	q9-12h	q12-18h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Meropenem	500 mg-2 g q8h	500 mg-1 g q12h	500 mg-1 g q24h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Metformin	100%	50%-avoid	Avoid	Avoid	Avoid	Avoid
Methadone	100%	100%	50%-75%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Methotrexate	100%	50%	Contraindicated	Contraindicated	Contraindicated	Dose as GFR 10-50
Methyldopa	q8h	q8-12h	q12-24h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Metoclopramide	100%	75%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50

Metocurine	75%	50%	50%	Unknown	Unknown	Dose as GFR 10-50
Mexiletine	100%	100%	50%-75%	Dose as GFR < 10	Dose as GFR < 10	As normal GFR
Midazolam	100%	100%	50%	Dose as GFR < 10	Dose as GFR < 10	As normal GFR
Midodrine	5-10 mg q8h	5-10 mg q8h	2.5-10 mg q8h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Milrinone	100%	100%	50%-75%	No data	No data	Dose as GFR 10-50
Mitomycin C	100%	100%	75%	Dose as GFR < 10	Dose as GFR < 10	As normal GFR
Mivacurium	100%	50%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Morphine	100%	75%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as < 10
Mycophenolate mofetil	100%	50%-100%	50%-100%	Dose as GFR < 10	Dose as GFR < 10	As normal GFR
N-Acetylcysteine	100%	100%	75%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Nadolol	q24h	q24-48h	q48h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Nalidixic acid	100%	Avoid	Avoid	Avoid	Avoid	Avoid
Neostigmine	100%	50%	25%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Netilmicin*	4-7.5 mg/kg/day	3-7.5 mg/kg/day	2 mg/kg/day	2 mg/kg after each	IV: 2 mg/kg q48h	Dose as GFR 10-50
Nicotinic acid	100%	50%	25%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Nitroprusside	100%	100%	Avoid	Avoid	Avoid	Dose as GFR 10-50
Nitrosoureas	100%	75%	25%-50%	Dose as GFR < 10	Dose as GFR < 10	Unknown
Nizatidine	75%-100%	50%	25%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Norfloxacin	q12h	q12-24h	q24h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Ofloxacin	100%	50%	25%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Oxcarbazepine	100%	75%-100%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Pancuronium	100%	50%	25%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Paroxetine	100%	50%-75%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Paraamino salicylic acid (PAS)	100%	50%-75%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Penicillamine	100%	Avoid	Avoid	Avoid	Avoid	Avoid
Penicillin G	100%	75%	20%-50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Pentamidine	q24h	q24h	q24-36h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Pentazocine	100%	75%	50%	Dose as GFR < 10	Unknown	Dose as GFR 10-50
Pentopril	100%	50%-75%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Pentoxifylline	q8-12h	q12-24h	q24h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Perindopril	2 mg q24h	2 mg q24-48h	2 mg q48h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Phenobarbital	q8-12h	q8-12h	q12-16h	Does as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Phenylbutazone	100%	50%	Avoid	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Pipecuronium	100%	50%	25%	Avoid	Avoid	Dose as GFR 10-50
Piperacillin	q6h	q6-12h	q12h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Plicamycin	100%	75%	50%	Unknown	Dose as GFR < 10	Dose as GFR 10-50
Pregabalin	100% q8-12h	50% q8-12h	25% q24h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Primidone	q12	q12-24h	q24h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Probenecid	100%	Avoid	Avoid	Avoid	Avoid	Avoid
Procainamide	q4h	q6-12h	q8-24h	Follow levels	Dose as GFR < 10	Dose as GFR 10-50
Propoxyphene	100%	100%	Avoid	Avoid	Avoid	Avoid
Propylthiouracil	100%	75%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Pyrazinamide	100%	100%	50%-100%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Pyridostigmine	100%	35%	20%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Quinapril	100%	2.5-5 mg q24h	2.5 mg q24h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Quinine	q8h	q8-12h	q24h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Ramipril	100%	50%	25%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Ranitidine	100%	100%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Ribavirin	100%	Avoid	Avoid	Avoid	Avoid	Avoid

Continued on following page

Table 84.8 Recommendations for Dosing Selected Drugs in Patients with Chronic Kidney Disease or Acute Kidney Injury (Continued)

	Degree of Drug Dose Reduction or Interval Prolongation			Dosage Recommendations for Patients Receiving Renal Replacement Therapy		
Drug	GFR > 50 mL/min	GFR = 10-50 mL/min	GFR < 10 mL/min	HD	CAPD	CRRT
Rifampin	100%	50%-100%	50%-100%	Dose as GFR < 10	Dose as GFR < 10	As normal GFR
Rivaroxaban	100%	Avoid	Avoid	Avoid	Avoid	Avoid
Simvastatin	100%	100%	10 mg q24h	Dose as GFR < 10	Dose as GFR < 10	As normal GFR
Sitagliptin	100%	50%	25%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Sotalol	100%	25%-50%	25%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Spironolactone	100%	50%	Avoid	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Stavudine	100%	50% q12-24h	50% q24h	Avoid	Avoid	Avoid
Streptomycin*	q24h	q24-72h	q72-96h	Dose as GFR < 10	20-40 mg/L/day	Dose as GFR 10-50
Streptozocin	100%	75%	50%	Unknown	Unknown	Unknown
Sulfamethoxazole	q12h	q18h	q24h	1 g after dialysis	1 g/day	Dose as GFR 10-50
Sulfinpyrazone	100%	100%	Avoid	Avoid	Avoid	Dose as GFR 10-50
Sulfisoxazole	q6h	q8-12h	q12-24h	2 g after dialysis	3 g/day	NA
Sulindac	100%	50%-100%	50%-100%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR < 10
Sulotroban	50%	30%	10%	Unknown	Unknown	Unknown
Tazobactam	100%	75%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Teicoplanin	q24h	q24-48h	q48-72h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Temocillin	q12-24h	q24h	q48h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Terbutaline	100%	50%	Avoid	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Tetracycline	100%	100%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Thiazides	100%	100%	Avoid	Dose as GFR < 10	Dose as GFR < 10	NA
Thiopental	100%	100%	75%	NA	NA	NA
Ticarcillin	50-75 mg/kg q6h	50-75 mg/kg q8h	50-75 mg/kg q12h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Tobramycin*	5-7 mg/kg/day	2-3 mg/kg/day	2 mg/kg q48-72h	3 mg/kg after HD	3-4 mg/L/day	Dose as GFR 10-50
Tolvaptan	100%	100%	Avoid	Avoid	Avoid	Avoid
Topiramate	100%	50%	25%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Topotecan	75%	50%	25%	Dose as GFR < 10	No data	No data
Tramadol	100%	50-100 mg q8h	50 mg q8h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Tranexamic acid	50%	25%	10%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Trazodone	100%	100%	Avoid/50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Triamterene	100%	Avoid	Avoid	Avoid	Avoid	Avoid
Trimethoprim	q12h	q12h	q24h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Trimetrexate	100%	50%-100%	Avoid	No data	No data	Dose as GFR 10-50
Tubocurarine	75%	50%	Avoid	Unknown	Unknown	Dose as GFR 10-50
Valganciclovir	50%-100%	450 mg q24-48h	450 mg Q72-96	Avoid	Avoid	450 mg q48h
Vancomycin*	1 g q12-24h	1 g q24-96h	1 g q4-7d	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Venlafaxine	100%	50%	50%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Vigabatrin	100%	50%	25%	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Zalcitabine	100%	q12h	q24h	Dose as GFR < 10	No data	Dose as GFR 10-50
Zidovudine (AZT)	100% q8h	100% q8h	50% q8h	Dose as GFR < 10	Dose as GFR < 10	Dose as GFR 10-50
Zileuton	100%	100%	100%	Dose as GFR < 10	Unknown	Dose as GFR 10-50

*Adjust dose to achieve desired serum concentrations using measured serum concentrations and pharmacokinetic modeling principles.
CAPD, Continuous ambulatory peritoneal dialysis; CRRT, continuous renal replacement therapy; HD, hemodialysis; NA, not applicable.

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